REMARKS/ARGUMENTS

Claims 36 to 49 are pending in the present application. All the claims stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Applicants note with appreciation that the rejection of claims for lacking written description has been withdrawn. The remaining rejection is respectfully traversed as explained below.

In the Office Action, the Examiner continues to reject the claims for allegedly lacking enablement based on assertions that the application is enabling only for C2 GlcNAcT null mice described there. The examiner asserts that other methods of inhibiting the activity of this enzyme *in vivo* (*e.g.*, by administration of inhibitors) require undue experimentation and are therefore not enabled.

As noted in previous rejection, the present invention is not the discovery of C2 GlcNacT inhibitors. Instead, the invention is the discovery that agents that have this function can be used in methods to inhibit inflammatory responses and still maintain immune system function. As explained in the specification and in the previous response, the use of inhibitors of glycosyltrasferases to treat disease was known in the art. Nothing in the Examiner's remarks appear to question the nature of the present invention or that inhibitors of glycosyltransferases were well known at the time of the invention.

In addition, applicants have previously provided a detailed review of the case law relating to inventions, such as this, that provide a new use for compounds known in the art. As explained there, the courts have specifically held that rejections under these facts are improper. Applicants respectfully submit that the present Office Action does not address these legal precedents.

In the present Office Action, the Examiner apparently takes the position that the pending claims require that C2 GlcNAcT be inhibited to the same level as that found in the C2 GlcNacT null mice (*see e.g.*, Office Action, page 4, lines 1-4). Since the mice completely lack the gene, no C2 GlcNAcT activity should be present in the mice. The Examiner points to nothing in the specification or the claims that supports this interpretation of the claims. In fact,

the specification makes clear that inhibition is used here to mean something other than simply 100% inhibition. For example, at page 23, lines 13-15 it is stated that the inhibitors of the invention preferably inhibit at least 75% of the enzyme's activity. Thus, there is no basis for reading the claims as limited to 100% inhibition.

On page 4, lines 12-14, of the Office Action, the Examiner acknowledges that *in vitro* testing of glycosyltransferase inhibitors continues to be actively investigated and advanced in the art. The Examiner alleges that the prior art shows that even *in vitro*, "candidate inhibitors of glycosyltransferases must be empirically tested." (page 4, line 15-16). Applicants, however, are not arguing that empirical *in vitro* testing is not necessary to identify inhibitors useful in the methods of the invention. Rather the applicants position is that testing of such compounds was well known in the art and was entirely routine at the time of the invention.

The case law is clear that the test of enablement is not whether ***any*** experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). As explained previously, methods for screening for glycosyltransferase inhibitors, including high through-put assays, are extensively discussed in the specification at pages 27-31. Moreover, high through-put screening assays specific for identifying C2 GlcNAcT inhibitors have been described (*see* Donovan *et al. Glyconjugate J.* 16:607-615 (1999), Exhibit A). Although this paper was published after the filing date of the present application, it demonstrates that developing such screens for this enzyme was well within the skill in the art at the time of the invention. The assay described there uses 96 well plates in high through-put assay as generally taught in the present specification (*see e.g.*, page 29, lines 14-25). As discussed on page 612 of that reference, a microbial library of 30,000 extracts was screened in the assay. As can be seen in Table 2 on page 613, 48 inhibitory compounds were identified in a primary screen of these extracts. After a secondary screen, 21 validated hits were identified. This reference demonstrates that the assay methods described in the present application can be used to identify inhibitors of C2 GlcNAcT, without undue experimentation. In light of this evidence, the Examiner cannot maintain the position that screening for inhibitors

using well known screening techniques, although time-consuming, was not entirely routine at the time of the invention.

The Examiner next takes the position that once an inhibitor is identified, it is "highly unpredictable" whether such a compound will have *in vivo* efficacy. For this proposition, the Examiner relies on Lowe *et al.* (Ref AI in applicants' IDS). In particular, the Examiner cites language on page 823 of Lowe *et al.* that allegedly supports the Examiner's position. In fact, the quoted language relates to the use of inhibitors of the interaction of selectins and their carbohydrate ligands, ***not*** inhibitors of glycosyltransferases.[1] Such inhibitors are a new class of inhibitory compounds that apparently had not been successfully used ***in vivo*** at the time.

This, however, is not true of glycosyltransferase inhibitors. As explained in the specification at page 21, lines 21-30, analogs of sugar nucleotides capable of inhibiting glycosylation have been used in the prior art as antibiotics and antiviral agents. Examples of such compounds include the antiviral compound 2-deoxy-D-glucose, as well as antibiotics such as tunicamycin (analog of UDP-GlcNAc) and streptovirudin. Thus, in contrast to the apparent uncertainties of blocking the interactions of selectins with their ligands, inhibitors of glycosyltransferases have a history of use *in vivo*. An assertion of the unpredictability of using glycosyltransferease inhibitors cannot be supported by that evidence.

Moreover, as demonstrated by the attached press release inhibitors of C2 GlcNAcT for the treatment of inflammation have been the focus of active research and development (Exhibit B). The attached press release from April, 2003 announces the purchase of Glycodesign by Inflazyme for $12.8 million. It is clear from the release that Glycodesign had developed inhibitors of C2 GlcNAcT that were a major part of the value obtained by Inflazyme. The first item identified as a rationale for the purchase is the fact that Glycodesign has developed novel Core 2 inhibitors. It should be noted that many of the authors of the Donovan paper

[1] As explained previously, the present invention is based, at least in part, on the discovery that C2 GlcNAcT is involved in the synthesis of the carbohydrate ligand of selectins, SLe^x.

discussed above were employees of Glycodesign. Thus, it is clear that the Glycodesign has an active research program identifying and testing inhibitors of C2 GlcNAcT for the treatment of inflammation. At least some portion of the purchase price of the company can be attributed to the value placed on the inhibitors that arose from this work. This is evidence that those of skill recognized that use of glycosyltransferase inhibitors *in vivo* for the treatment of inflammation was not entirely unpredictable as is asserted by the Examiner.

In conclusion, the Examiner has failed to provide sufficient reasoning and evidence to show that *in vitro* assays cannot be used to identify C2 GlcNAcT inhibitors. In fact, the Donovan *et al.* publication demonstrates that the screening assays described in the specification can be used to identify such inhibitors without undue experimentation. The Examiner has also attempted to show the unpredictability of *in vivo* efficacy by citing a reference discussing a class of inhibitors different from those claimed here. Indeed, the class of inhibitors used in the present invention have been used therapeutically *in vivo* in the prior art. Finally, applicants provide evidence that C2 GlcNAcT inhibitors are the subject of a very valuable research and development program. In light of the above, the Examiner has failed to show that undue experimentation would be required to make and use C2 GlcNAcT inhibitors for the treatment of inflammation. Applicants respectfully submit that the current rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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